THE LANCET Respiratory Medicine

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Calfee CS, Delucchi K, Parsons PE, et al. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med* 2014; published online May 20. http://dx.doi.org/10.1016/S2213-2600(14)70097-9.

ONLINE SUPPLEMENTARY MATERIALS

Latent Class Analysis of ARDS Subphenotypes: Analysis of Data From Two Randomized Controlled Trials

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Additional Detail Regarding Original Trials

The original trials were approved by the institutional review boards at each participating hospital; informed consent was obtained from the patients or surrogates at all but one hospital in the ARMA cohort, where this requirement was waived. Patients were followed until discharge home, death, or at least 90 days in both studies. Both the lisofylline and ketoconazole studies within the ARMA cohort were negative studies, with no evidence of treatment effect on clinical outcomes. The ARDS Network provided approval for the use of the data for this project.

Additional Detail Regarding Statistical Methods

Prior to beginning the analysis, the baseline clinical variables were examined jointly by two study investigators (CSC, KD) to cull variables with a high proportion of missing data and/or variables that were highly collinear and/or redundant (e.g. peak and nadir serum sodium from day of randomization). Additionally, variables that were coded as positive in less than 10% of cases (e.g. the acquired immunodeficiency syndrome, leukemia, lymphoma) were excluded from the analyses.

For the latent class models, since the scales of each measure varied widely, all continuous measures were rescaled to a common z-scale where the mean was set to 0 and the standard deviation to 1 within each cohort. Of note, we excluded APACHE III score from the latent class models since it is derived from the other clinical variable inputs; re-fitting the models including APACHE produced very similar results (data not shown). To avoid a local maximum likelihood solution, we used 100 random starting values, of which the best 20 were then optimized. Those solutions were checked to ensure the same maximum likelihood was found.

As an indicator of how distinct the classes were from each other, we also measured the average of the latent class probabilities for each class: that is, for a given model, the likelihood of belonging to each class for a given subject. In an exploratory analysis to determine whether a reduced handful of variables could accurately classify patients, we used the measures with the greatest difference in mean absolute values between latent classes in the ARMA cohort as covariates in a set of three nested logistic regression models predicting latent class in both cohorts.

Table S1: Complete List of Clinical Variables Included in LCA Models After Data Cleaning

Clinical Variables	Number of Patients With Data, ARMA Cohort (total n=473)	Number of Patients with Data, ALVEOLI Cohort (total n=549)	Number of patients with missing data, both cohorts (total n=1022)
Heart rate (highest)	473	548	1
Minute Ventilation	469	544	9
Mean airway pressure	396	515	111
Plateau pressure	369	436	217
Creatinine (highest)	446	547	22
Respiratory rate (highest)	473	548	1
Positive end-expiratory pressure	473	546	3
Total bilirubin	428	516	78
Temperature (highest)	473	548	1
Hematocrit (lowest)	470	548	4
Urine output over prior 24h	451	527	44
White blood cell count (highest)	447	545	30
Sodium (lowest)	464	548	10
Body Mass Index	441	505	76
Age in years	473	549	0
Tidal volume	327	507	188
Glucose (lowest)	463	545	14
PaO2/FiO2 ratio (qualifying)	472	549	1
Albumin (lowest)	411	514	97
Platelets	468	544	10
PaCO2	439	524	59
Systolic blood pressure (lowest)	472	548	2
Bicarbonate	469	548	5
Gender (M/F)	473	549	0
Race-ethnicity (Caucasian vs. other)	473	549	0
Vasopressors (Y/N)	338	549	135
Etiology of ARDS (Trauma, Sepsis, Aspiration, Pneumonia or Other)	461	522	39

Table S2: Area Under the Curve (AUC) values for nested logistic regression models predicting most likely latent class.

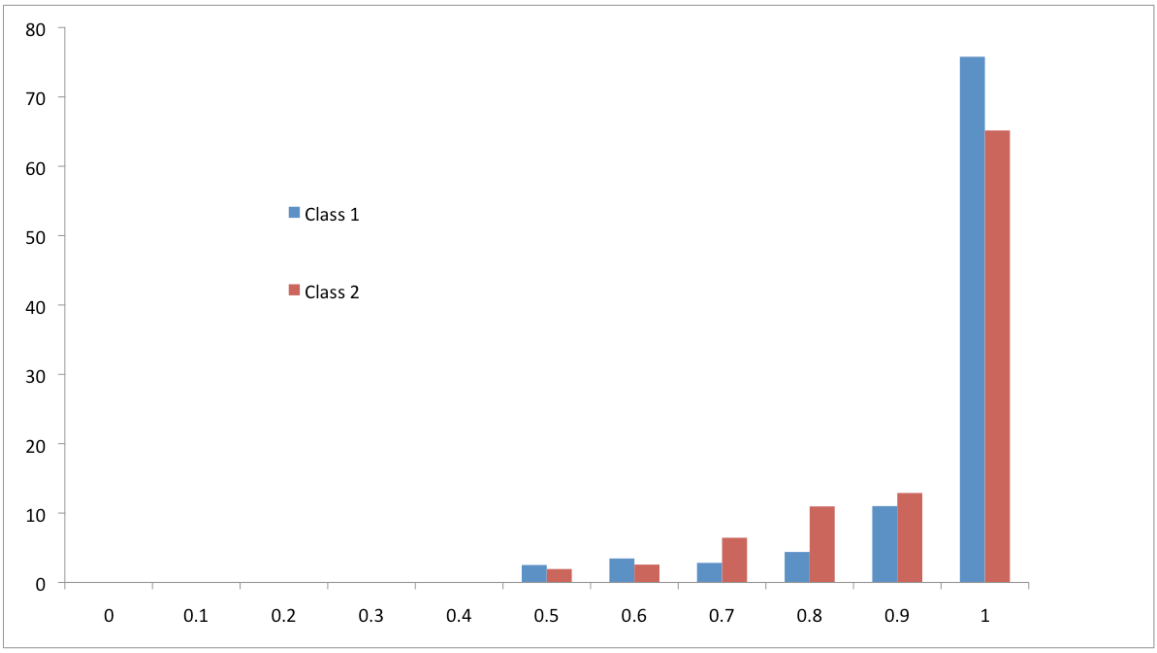
Predictors	Derivation Cohort	Replication Cohort
IL-6 plasma level, sTNFr-1 plasma level, Vasopressor use (Y/N)	.937	.929
As above plus IL-8 plasma level	.952	.959
As above plus plasma bicarbonate	.973	.967

Table S3: Association between Phenotype Assignment and Clinical Outcomes, Unadjusted

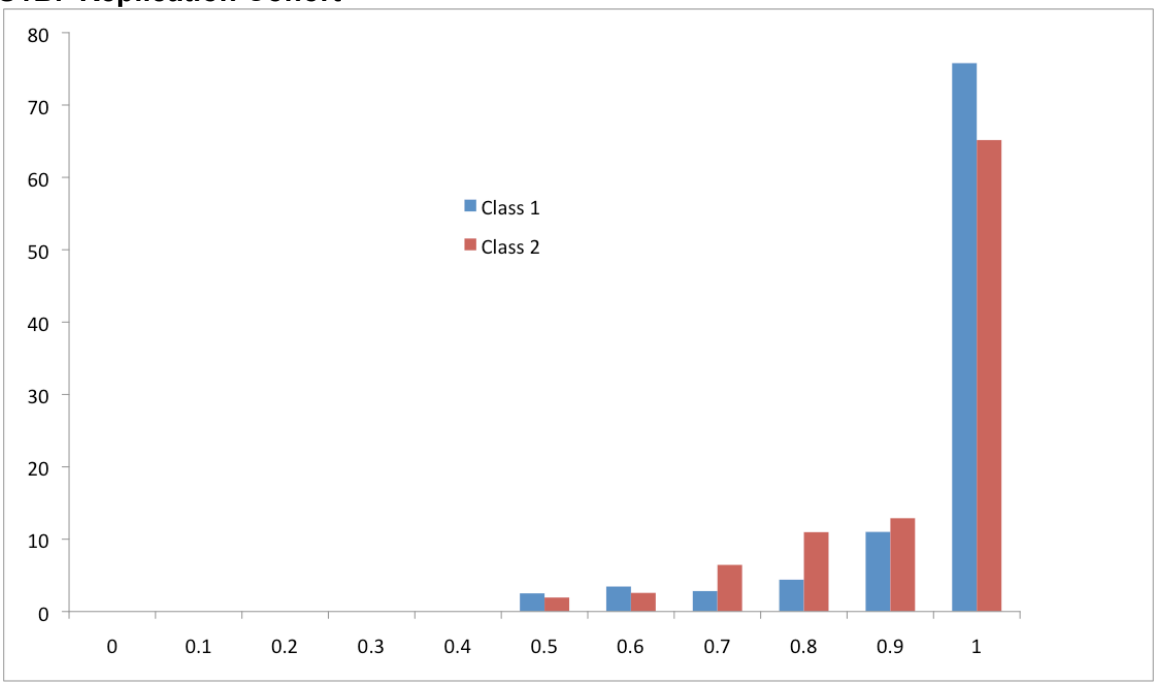
	ARMA Cohort			ALVEOLI Cohort		
Clinical Outcome	**Phenotype 1 (n=318)**	**Phenotype 2 (n=155)**	**p-value**	**Phenotype 1 (n=404)**	**Phenotype 2 (n=145)**	**p-value**
Ventilator Free Days, Mean	14.0	9.1	<0.001	16.3	8.8	<0.001
Organ Failure Free Days, Mean	16.8	9.8	<0.001	17.9	8.7	<0.001
Mortality (90-day)	25%	40%	0.012	20%	48%	<0.001

Figure S1: Probabilities of Class Assignment. Figures show probability of belonging to the class to which the subject was assigned, by decile of probability.

S1A. Derivation Cohort



S1B. Replication Cohort



ACKNOWLEDGEMENTS

NATIONAL INSTITUTES OF HEALTH

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE ARDS NETWORK

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